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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,859	HUANG ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *20-43,45 and 47-69* is/are withdrawn from consideration.

5)☒ Claim(s) *7 and 8* is/are allowed.

6)☒ Claim(s) *1-6,9-11,13-19,44 and 46* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20030603*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The election filed October 27, 2004, is acknowledged and has been entered. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has elected the invention of Group I, claims 1-19, 44, and 46, drawn to a nucleic acid, an expression cassette comprising the polynucleotide sequence of the nucleic acid, a transformed cell comprising the nucleic acid molecule, an array comprising the nucleic acid molecule, and a method for producing a polypeptide comprising expressing the nucleic acid.

2. Claims 1-69 are pending in the application. Claims 20-43, 45, and 47-69 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

3. Claims 1-19, 44, and 46 are currently under prosecution.

Information Disclosure Statement

4. The information disclosure filed March 3, 2003 has been considered. An initialed copy is enclosed.

Specification

5. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include GenBank™ (page 7, line 10) and Lipofectin™ (page 29, line 13).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

6. The disclosure is objected to for the following reason: The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, numerous sequences are disclosed in the specification, which are not identified by sequence identification numbers, including those sequences disclosed at page 8, line 9; page 8, line 13; page 8, line 13; page 29, lines 3 and 4; page 31, lines 20-54 (i.e., the "coding region nucleotide sequence"); page 34, line 12; page 35, line 2; page 35, line 4; page 35, line 18; and page 35, line 26.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must

submit paper and computer-readable copies of a substitute sequence listing, together with a statement that the content of both copies are the same and, where applicable, include no new matter.

7. The disclosure is objected to because of the following informalities:

(a) At page 28, line 28, "1999" has been mistyped as "19999".

(b) At page 16, lines 14 and 15, the specification discloses, "[i]f a polynucleotide sequence has the requisite sequence identity to SEQ ID NO:2..."; however, since SEQ ID NO: 2 is an amino acid sequence, the disclosure should read: "If an amino acid sequence has the requisite sequence identify to SEQ ID NO: 2...".

Appropriate corrections are required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 9-11, 13-18, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Claims 1, 9-11, 13-18, 44, and 46 are directed to a nucleic acid molecule comprising a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1.

Although the claimed nucleic acid molecule must have a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, this common structural property of the nucleic acid molecules encompassed by the claims does not necessarily relate to any particularly identifying functional feature of either the nucleic acid molecules or their translation products, i.e., the proteins encoded thereby.

Although a nucleic acid molecule comprising SEQ ID NO: 1 encodes a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 2, a nucleic acid molecule comprising a polynucleotide sequence that is not identical to SEQ ID NO: 1, but only at least 95% identical, does not necessarily encode a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or a variant of the polypeptide of SEQ ID NO: 2, which has or retains any particularly identifying functional property of the polypeptide of SEQ ID NO: 2.

Giving the claims the broadest reasonable interpretation, therefore, the claims are directed to a genus of nucleic acid molecules, which includes members that vary markedly in function, since the members encode polypeptides that vary in both structure and function.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an

adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

The specification provides an adequate written description of nucleic acid molecules that comprise SEQ ID NO: 1; it also provides an adequate written description of the polypeptide of SEQ ID NO: 2, which is encoded by SEQ ID NO: 1.

However, because the members of the claimed genus of nucleic acid molecules merely comprise a nucleotide sequence that is at least 95% identical to SEQ ID NO: 1, the members are not necessarily functionally related to the nucleic acid molecule of SEQ ID NO: 1, since the polypeptide encoded by the claimed nucleic acid molecule does not necessarily have same structure and function as the polypeptide encoded by SEQ ID NO: 1 (i.e., the polypeptide of SEQ ID NO: 2).

The adequate description of one member of the claimed genus of nucleic acid molecules is not sufficient to meet the requirements of 35 USC § 112, first paragraph, since the genus embraces variant members and an adequate description of such a genus cannot be achieved by describing members, which are not necessarily representative of the genus. As claimed, the genus of nucleic acid molecules does not solely embrace members having a common functional

feature shared by at least a substantial number of its members, the presence of which correlates with a property of the recited structural feature. As such, absent factual evidence of an actual reduction to practice, as discussed above, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the claimed genus. Accordingly, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

This issue may is remedied by amending the claims, such that the breadth of the claims is limited to a nucleic acid comprising SEQ ID NO: 1, or alternatively to a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1 and encoding a polypeptide comprising SEQ ID NO: 2 or a polypeptide having or retaining a disclosed, particularly identifying functional property of the polypeptide of SEQ ID NO: 2 that correlates with a particularly identifying structural feature common among the members of the genus of polypeptides encoded by the nucleic acid molecule of SEQ ID NO: 1 and the other nucleic acids also encompassed by the claims.

10. Claims 1-6, 9-11, 13-19, 44, and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1 and encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, an expression cassette comprising the polynucleotide sequence of said nucleic acid molecule, an isolated transformed cell comprising said nucleic acid molecule, an array comprising said nucleic acid molecule, and a method for producing a recombinant polypeptide comprising the amino acid sequence of SEQ ID NO: 2 comprising expressing said nucleic acid molecule, **does not reasonably provide enablement for making and using** a nucleic acid molecule comprising a sequence that is not identical to SEQ ID NO: 1 or encoding a polypeptide comprising an amino acid sequence that is not identical to SEQ ID NO: 2, or an expression cassette comprising the

polynucleotide sequence of said nucleic acid molecule, or a transformed cell comprising said nucleic acid molecule, an array comprising said nucleic acid molecule, or a method for producing a recombinant polypeptide comprising expressing said nucleic acid molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is a scope of enablement rejection.

The amount of guidance, direction, and exemplification disclosed by Applicant would not be sufficient to enable the skilled artisan to make and/or use the claimed invention without a need to perform an undue amount of additional experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification teaches the polypeptide of SEQ ID NO: 2 is encoded by an isolated nucleic acid molecule comprising the polynucleotide sequence set forth as SEQ ID NO: 1; see, e.g., page 32, lines 19-21; and Figure 1B. The specification discloses that the polypeptide of SEQ ID NO: 2 inhibits the activity of caspase-9, which, in turn, can inhibit the onset of apoptosis when expressed recombinantly in certain cells; see, e.g., page 32, line 34, through page 36, line 2.

Claims 1-6 are drawn to a genus of nucleic acid molecules that comprise a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1; claims 9-

11 are drawn to a genus of expression cassettes comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1; claims 13-18 are drawn to a genus of transformed cells comprising a nucleic acid sequence having at least 95% identity to SEQ ID NO: 1; claim 44 is drawn to an array comprising a nucleic acid having a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1; and claim 46 is drawn to a genus of methods for producing polypeptide comprising expressing a nucleic acid having a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1.

Claims 7, 8, 12, and 19 are directed to a genus of nucleic acids that encode a polypeptide comprising the amino acid sequence set forth as SEQ ID NO: 2. In contrast, claims 1-6, 9-11, 13-18, 44, and 46 encompass nucleic acids that do not necessarily encode a polypeptide comprising the amino acid sequence of SEQ ID NO: 2. Furthermore, while claims 2-8, 12, and 19 are directed to a genus of nucleic acids that encode a polypeptide (e.g., the polypeptide of SEQ ID NO: 2) that is capable of inhibiting apoptosis in insect cells, mammalian cells, or plant cells, or a polypeptide that is capable of inhibiting caspase-9, claims 1, 9-11, 13-18, 44, and 46 are not limited to nucleic acid molecules encoding a polypeptide having any particular function.

Accordingly, claims 1-6, 9-11, 13-18, 44, and 46 are directed to a genus of nucleic acids that comprise a polynucleotide sequence, which is least 95% identical to SEQ ID NO: 1, but which either does or does not encode a protein, does or does not encode a protein comprising the amino acid sequence of SEQ ID NO: 2, or does or does not encode a protein capable of inhibiting the incidence of apoptosis or the activity of caspase-9.

Claims 1, 9-11, 13-18, 44, and 46 are not limited to nucleic acid molecules encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or a polypeptide having any particular function, such as the ability to inhibit the

proteolytic activity of caspase-9. Although methods for isolating other nucleic acid molecules comprising polynucleotide sequences that are at least 95% identical to SEQ ID NO: 1 are conventional in the art (e.g., hybridization assays), because the claims are not limited to nucleic acid molecules encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or a polypeptide having any particular function, and the protein encoded by the nucleic acid does not have or retain the function of the polypeptide of SEQ ID NO: 2, the skilled artisan would be left to discover a use for the claimed invention. Discovering a use for claimed nucleic acid molecule that does not encode the polypeptide of SEQ ID NO: 2 or a polypeptide that has or retains the function of the polypeptide of SEQ ID NO: 2 falls into the realm of undue experimentation, since one would first have to characterize the activity or function of the nucleic acid or the protein encoded by the nucleic acid and then to develop methods for using the nucleic acid or protein, depending upon its activity or function.

Claims 2-6 are directed to a genus of nucleic acids that encode a polypeptide that is capable of inhibiting apoptosis in insect cells, mammalian cells, or plant cells, or a polypeptide that is capable of inhibiting caspase-9, but are not limited to nucleic acid molecules encoding a polypeptide comprising SEQ ID NO: 2. However, not all polypeptides encoded by members of the genus of nucleic acid molecules having a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, even those that are substantially similar to the polypeptide of SEQ ID NO: 2, are reasonably expected to have a function that is equivalent to the function of the polypeptide of SEQ ID NO: 2.

Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure

between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2).

In addition, Bowie et al. (*Science* **257**: 1306-1310, 1990) teaches that an amino acid sequence encodes a message that determines the shape and function of a protein; and, that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome. Bowie et al. teaches that the determination of protein structure from sequence data and, in turn, utilizing structural determinations to ascertain functional aspects of the protein is extremely complex (page 1306, column 1). Even if the skilled artisan were able to submit a complete list of the possible nucleic acids and the proteins encoded thereby, which fall within the scope of the claims, the skilled artisan could not recognize which of these would function similarly to a protein comprising SEQ ID NO: 2, and which would not.

Thus, one skilled in the art would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a variant of the polypeptide of SEQ ID NO: 2 is functionally equivalent to the polypeptide of SEQ ID NO: 2, or even has a structure that is substantially equivalent to that of the polypeptide of SEQ ID NO: 2.

In addition, although the polypeptide of SEQ ID NO: 2 is disclosed as having the ability to inhibit caspase-9 and thereby inhibit the incidence of apoptosis in certain cells, the specification does not describe which amino acid residues of the polypeptide of SEQ ID NO: 2 are essential to that activity or which must be retained to preserve that activity. Moreover, the specification does not teach which amino acids in the sequence of the polypeptide can be replaced, and by which other amino acids, without a loss of that activity. Again, as evidenced by the teachings of Skolnick et al. and Bowie, for example, the skilled artisan cannot accurately and reliably predict whether a given homologue of a particular protein known to have a certain activity will also have that activity. In addition, the skilled artisan cannot reliably and accurately predict the functional

and structural consequences of amino acid differences; but the more structurally disparate a given protein, the less likely the protein will share the function of structurally related proteins having known functions. Burgess et al. (*Journal of Cell Biology* 1990; **111**: 2129-2138) exemplifies the sensitivity of proteins to alterations of even a single amino acid in a sequence. Burgess et al. teaches that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. As another example of this sensitivity to amino acid sequence variations, Lazar et al. (*Molecular and Cellular Biology*, 1988, **8**: 1247-1252) teaches that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect but that a replacement with serine or glutamic acid sharply reduced its biological activity. Thus, Lazar et al. teaches that even a single *conservative* type amino acid substitution may adversely affect the function of a protein.

Consistently, Luque et al. (*Biochemistry.* 2002 Nov 19; **41** (46): 13663-13671) reported that substitution of a single highly conserved amino acid in baculovirus *Orgyia psuedotsugata* Op-IAP and *Drosophila* DIAP1 abolishes the function of the proteins, as defined by their ability to bind apoptosis stimulators, including *Drosophila* Hid and mammalian Smac/DIABLO; see entire document (e.g., the abstract). Although the amino acid replaced is highly conserved and might therefore have been reasonably expected to be essential to the function of the protein, because the inhibitor of apoptosis proteins have more than one specific activity, some residues, which although conserved, may not be important to specific activities, whereas others are. The skilled artisan cannot predict which conserved amino acid residues are critical to which specific activities of such multifunctional proteins. For example, Vucic et al. (*J. Biol. Chem.* 1998 Dec 18; **273** (51): 33915-33921) performed a mutational analysis of baculovirus inhibitor of apoptosis Op-IAP and found that, although most of the conserved amino acid residues in the BIR2 motif were revealed to be essential to the protein's ability to inhibit apoptosis, most of these conserved residues were not required for binding

to Hid; see entire document (e.g., the abstract). A region at the carboxy-proximal end of BIR2 was essential for binding to Hid (apoptosis). Vucic et al. disclose that these results show that binding to Hid is necessary but not sufficient to block Hid-induced apoptosis (abstract). Thus, while it is possible to determine which amino acids residues are conserved in various different family members, it is not possible to predict which of these conserved residues are critical to the various different functions of a multifunctional protein.

Echoing this fact, Takada et al. (*Mol. Endocrinol.* 2000; **14** (5): 733-740) teaches that the lack of predictability in the art remains, despite technological advances and a better understanding of the structure-function relationship; see entire document (e.g., the abstract). Takada et al. teaches their work illustrates that a single amino acid change may be sufficient to cause the acquisition of a new ligand binding specificity as well as to suppress recognition of a previous ligand, extending observations by others who showed that changes in one or several amino acids can result in marked alterations in activity and function of nuclear receptors (page 738, column 1). Notably, Takada et al. teaches that the functional consequence of amino acid substitution may be rather subtle, since the variants of the receptors were still able to bind to the promoter of the reporter construct and activate transcription in the presence of some ligands but not others; see, e.g., page 739, Figure 5. Takada et al. teaches the difference in ligand binding specificity caused by the amino acid changes results in the variants having the activity of different member of the family of proteins; see, e.g., the abstract. Thus, Takada et al. discloses that seemingly subtle differences resulting from amino acid differences, such as changes in ligand binding specificity, may cause variants of a protein to have a function that differs markedly from that of the protein. Accordingly, depending upon the assay used to assess the activity of the proteins and its variants, the effects of amino acid sequence variation may not be immediately recognized or appreciated, since the variants may appear to function normally otherwise, but in actuality have substantially different functions.

Even more recently, Guo et al. (*Proc. Natl. Acad. Sci. USA*. 2004 Jun 22; **101** (25): 9205-9210) have calculated the probability that a random amino acid substitution, such as that which might occur naturally during aging or as a consequence of evolution or disease, will cause inactivation of a protein; see entire document (e.g., the abstract). Guo et al. reports this probability was found to be 34% ± 6% (abstract); that is, 34% of random mutations in the sequence of a protein are predicted to cause the inactivation of the protein. Guo et al. observed that various residues are differentially sensitive to substitutions, but the tolerance of the entire protein to random change can be defined by the probability that any given random amino acid substitution will inactivate the protein (i.e., the so-called "*x* factor") (page 9209, column 2). Not surprisingly, evolutionarily conserved residues showed low substitutability indices (abstract).

Thus, Lazar et al., for example, shows that even a single, conservative amino acid change can cause substantial changes in the activity of a protein, so it is evident that the skilled artisan cannot predict the functional consequences of amino acid substitutions and must determine those consequences empirically; and since Guo et al. shows that amino acid substitutions are remarkably likely to cause inactivation of the protein, it is even more apparent that the functional consequences of the amino acid differences must be ascertained before any given variant of a protein can be used in the same manner in which the protein having a known function is used.

Claims 2-6 are directed to a genus of nucleic acids that encode a polypeptide that is capable of inhibiting apoptosis in insect cells, mammalian cells, or plant cells, or a polypeptide that is capable of inhibiting caspase-9, including nucleic acid molecules encoding a polypeptide comprising SEQ ID NO: 2. However, Huang et al. (*Biochim. Biophys. Acta*. 2001 Jan 15; **1499** (3): 191-198) (of record) teaches that, while the polypeptide of SEQ ID NO: 2 is capable of inhibiting apoptosis in *Spodoptera frugiperda* Sf-21 insect cells induced by p35-deficient *Autographa californica* nucleopolyhedrovirus (AcMNPV) and of inhibiting apoptosis in mammalian cells induced by Bax, it is not capable of

inhibiting apoptosis in mammalian cells induced by Fas; see entire document (e.g., the abstract). Similarly, the specification teaches that the polypeptide of SEQ ID NO: 2 is capable of inhibiting Bax-induced apoptosis in mammalian cells, but incapable of inhibiting Fas-induced apoptosis (page 34, lines 3-5).

The specification discloses that the polypeptide of SEQ ID NO: 2 is a member of a family of "inhibitor of apoptosis" proteins (IAPs); see, e.g., page 32, line 19, through page 33, line 2. The specification discloses that, similar to other members of the family of IAPs, the polypeptide of SEQ ID NO: 2 (i.e., BmIAP) contains two BIR domains followed by a RING domain near the carboxy-terminus; see, e.g., Figure 1. The specification teaches that there is variable conservation of the amino acid sequence in the region of the protein comprising these domains; for example, the region is 88% identical to the corresponding region in *Spodoptera frugiperda* IAP (SfIAP) (page 34, lines 34-39).

The specification discloses that since SfIAP is capable of inhibiting Bax-induced apoptosis in mammalian cells, it was perhaps expected that BmIAP would also be capable of such activity; see page 34, lines 14-21. However, unlike both SfIAP and BmIAP, the specification teaches that mammalian XIAP is capable of inhibiting apoptosis induced by both Bax and Fas (page 34, lines 21 and 22). Therefore, the various different members of the family of IAPs, which are the counterparts of BmIAP in other organisms, are not functionally equivalent to BmIAP or SfIAP.

Huang et al. (cited *supra*) also teaches that, although the various different members of the family of IAPs contain one to three copies of the BIR domain and most contain a RING domain near the carboxy-termini (page 192, column 1), the IAPs are not functionally equivalent. Despite sharing such evolutionarily conserved domains, Huang et al. teaches that BmIAP and SfIAP did not inhibit caspase-3 and caspase-7, whereas XIAP did (page 196, column 1). Furthermore, Huang et al. teaches another members of the family, *Autographa californica* IAP (AcIAP) is ineffective at inhibiting apoptosis in both mammalian and insect cells (page 194, column 1).

Furthermore, despite the evident structural homology among family members, the specification teaches that both BIR and RING domains of BmIAP are essential to the ability of the protein to block apoptosis induced by p35-deficient AcMNPV in insect cells (page 33, lines 3 and 4), whereas Takahashi et al. (*J. Biol. Chem.* 1998 Apr 3; **273** (14): 7787-7790) teaches only the BIR domains of XIAP are required to inhibit Fas-induced apoptosis, and only a single BIR domain is sufficient for binding to caspase-3 and caspase-7 and for partially inhibiting apoptosis (see entire document, e.g., the abstract).

These teachings, together with the other references cited to illustrate the unpredictability associated with amino acid sequence variation. These references show that the skilled artisan cannot predict whether a variant of the polypeptide of SEQ ID NO: 2, which is encoded by a member of the claimed genus of nucleic acid molecules comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, is capable of inhibiting apoptosis induced by any particular stimulus, since the polypeptide of SEQ ID NO: 1 is capable of inhibiting Bax-induced apoptosis, but not Fas-induced apoptosis, and despite containing BIR and RING domains, the different members of the family of IAPs have different abilities to inhibit the activities of various different caspases and have different abilities to inhibit the incidence of apoptosis induced by various different stimuli.

Further regarding this latter issue of predictability, Abraham et al. (*Trends Cell Biol.* 2004 Apr; **14** (4): 184-193), for example, teaches that there are cell death processes, which are "caspase-independent"; see entire document (e.g., the abstract). While the polypeptide of SEQ ID NO: 2 is capable of inhibiting caspase-9, because apoptosis can evidently occur in a manner that is independent of caspase activation, the polypeptides encoded by the claimed nucleic acid molecules may not be capable of inhibiting caspase-independent apoptosis. Since it cannot be predicted whether these polypeptides are capable of such activity, and it can only be determined empirically, the skilled artisan could not use the claimed invention without having to perform undue

experimentation, because the invention cannot be used until the determination has been made.

Claim 5 is drawn to a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 2, which encodes a polypeptide capable of inhibiting apoptosis in a genus of plant cells; and claim 2 is drawn to a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 2, which encodes a polypeptide capable of inhibiting apoptosis in a genus of insect cells. However, the specification merely teaches that the polypeptide of SEQ ID NO: 2 (BmIAP) is capable of inhibiting apoptosis induced by p35-deficient AcMNPV in *Spodoptera frugiperda* Sf-21 cells, of inhibiting apoptosis induced by Bax, but not Fas, in mammalian HEK293 cells, and of inhibiting caspase-9 in a cell-free system (pages 33-36). Because the polypeptide of SEQ ID NO: 2 occurs in *Bombyx mori* (silkworm) cells, it is reasonable to presume, absent any factual evidence showing otherwise, that the polypeptide is capable of inhibiting apoptosis in *Bombyx mori* cells, especially since the specification discloses that the protein is capable of inhibiting apoptosis in the cells of another lepidopteran, namely *Spodoptera frugiperda*. However, insects are highly divergent and there is no factual evidence of record that the polypeptide of SEQ ID NO: 2 is capable of inhibiting apoptosis in other insects, particularly non-lepidopteran insects, such as, for example, *Drosophila melanogaster* (fruit fly). Similarly, there is no factual evidence of record that the polypeptide of SEQ ID NO: 2 or any variant thereof encoded by a member of the claimed genus of nucleic acid molecules is capable inhibiting apoptosis in plant cells, but because plants are even less similar to *Bombyx mori* than other insects, the skilled artisan would not reasonably accept the assertion that the polypeptide of SEQ ID NO: 2 is capable of inhibiting apoptosis in plant cells.

Yu et al. (*FEBS Lett.* 2002 Feb 13; **512** (1-3): 308-312), for example, provides factual evidence that it cannot predicted whether the polypeptide of SEQ ID NO: 2 is capable of inhibiting apoptosis in plant cells and other non-lepidopteran insects. Yu et al. teaches a plant Bax inhibitor, which is an

orthologue of mammalian Bax inhibitor-1; see entire document (e.g., the abstract). Although the mammalian Bax inhibitor-1 (BI-1) inhibits apoptosis induced by Bax in mammalian cells and when ectopically expressed, is capable of inhibiting apoptosis in yeast, the plant *Arabidopsis thaliana* Bax inhibitor-1 orthologue (AtBI-1) is not; in fact, in complete contrast, rather than inhibiting apoptosis, the protein when expressed in mammalian cells induces their apoptotic cell death; see, e.g., page 308, column 2.

Furthermore, in plants, "programmed cell death" or "apoptosis", which terms the specification does not evidently distinguish (see, e.g., page 8, lines 21-23), is a rather disparate process compared to that which occurs in metazoans. Kuriyama et al. (*Curr. Opin. Plant Biol.* 2002 Dec; **5** (6): 568-573) compares and contrasts some of the morphologic, physiologic, and biochemical characteristics of the processes that occur in plants and animals; see entire document (e.g., page 569, Figure 1). Accordingly, despite some evolutionary conservation, these processes are in plants and animals different. As Kuriyama et al. teaches, these differences are underscored by, for example, the absence of othologous counterparts in plants and animals (page 570, column 2), or the presence of othologues having markedly different functions, such as those described by Yu et al. (*supra*).

Accordingly, because it cannot be predicted whether the polypeptide of SEQ ID NO: 2 or a variant thereof that is encoded by a nucleic acid molecule comprising a polynucleotide sequence that is at least 95% identical to SEQ ID NO: 1, the functional capability of the proteins can only be determined empirically. Determining whether these protein encoded by the claimed invention are capable of inhibiting apoptosis in various different cells, including plant cells, insect cells, and mammalian cells, which is necessary before the invention can be used, constitutes additional, undue experimentation.

Claims 13, 14, 17, and 19 are drawn to transformed cells comprising a nucleic acid molecule that is at least 95% identical to SEQ ID NO: 1, including mammalian and plant cells. The claims are broadly interpreted to encompass

transformed host cells, which are not isolated and are comprised within an organism. Thus, the claims encompass host cells that have been transfected with a nucleic acid molecule, which are comprised within an animal or plant including non-human transgenic animals or transgenic plants.

The specification discloses that nucleic acid molecules and vectors encoding SEQ ID NO: 2 or variants thereof can be used to produce transgenic animals and plants that express the polypeptide; see, e.g., page 22, line 7, through page 24, line 4.

However, the specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use host cells that are comprised within a non-human transgenic animals and plants. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predictable; nor is the transgenic embryo always viable. Houdebine (*Journal of Biotechnology* 1994, 34: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions; see entire document (e.g., paragraph bridging pages 272 and 273). Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable (page 27, column 1). Therefore, it is concluded that one of skill in the art would need to perform additional, undue experimentation in order to make and use the claimed host cell comprised within a transgenic animal.

Similarly, in the art of producing transgenic plants, the phenotype of the resultant transgenic plant is not always predictable and furthermore there are difficulties in relating gene function to an observed phenotype. For example, Ayliffe et al. (*Mol. Plant Microbe Interact.* 2004 Aug; **17** (8): 853-864) teaches the success of gene transfer between plant species is limited not only by divergence of signaling effector molecules and pathogen avirulence ligands, but also by more fundamental gene expression and transcript processing limitations; see entire document (e.g., the abstract). The significant issues and hurdles to

successful production and use of transgenic plants have been reviewed by Day (*Am. J. Clin. Nutr.* 1996 Apr; **63** (4): 651S-656S). Among the limitations, Day teaches there is little or no control of copy number or site of intergretion of the introduced DNA, dependence on selectable markers for recovery of traits and inadequate knowledge of how to control key metabolic steps to maximize desirable traits; see entire document (e.g., the abstract). More recently, Cellini et al. (*Food Chem. Toxicol.* 2004 Jul; **42** (7): 1089-1125) teaches that one of the most significant limitations to the technology, which still hampers success, are unintended effects and their detection in genetically modified crops; see entire document (e.g., the abstract). One of these unintended effects is the inadvertent production of toxicants and allergens.

Thus, the specification provides only a sufficient amount of guidance and direction to enable the skilled artisan to make and use an *isolated* transformed cell, which is *not* a transformed cell comprised within a transgenic plant or animal.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

Claim Rejections – 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 13, 15, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Fatyol et al. (*Mol. Gen. Genet.* 1998 Oct; **260** (1): 1-8), as evidenced by Huang et al. (*Biochim. Biophys. Acta*. 2001 Jan 15; **1499** (3): 191-198) (of record), the USPTO search report "us-10-041-859-2.rge" (result 1 of the "Alignments"), and the USPTO search report "us-10-041-859-1.rge" (result 1 of the "Alignments").

Claims 13, 15, and 19 are drawn to a transformed cell comprising a nucleic acid sequence having at least 95% identity to SEQ ID NO: 1 (claim 13), wherein said cell is an insect cell (claim 15) or wherein said nucleic acid encodes a polypeptide having the amino acid sequence of SEQ ID NO: 2 (claim 19).

The specification defines the term "nucleic acid sequence" or "nucleic acid" as "a deoxyribonucleotide or ribonucleotide oligonucleotide, including single- or double-stranded forms, and coding or non-coding (e.g., 'antisense') forms" (page 12, lines 4-6). Additionally, the specification discloses that the term "nucleic acid" is used interchangeably with gene, DNA, RNA, cDNA, mRNA, oligonucleotide primer, probe, and amplification product" (page 12, lines 23 and 24). Accordingly, although the polynucleotide sequence that is listed as SEQ ID NO: 1 is a deoxyribonucleotide (DNA) sequence, the claim does not certainly exclude a ribonucleotide (RNA) sequence that is complementary to SEQ ID NO: 1 and representative of the non-coding sequence (e.g., the polynucleotide sequence of a messenger RNA (mRNA) encoding the same amino acid sequence as the deoxyribonucleotide sequence of SEQ ID NO: 1).

The specification defines the term percent "sequence identity" as referring to the two or more sequences or subsequences that are the same or have a specified percentage of nucleotides [...] that are the same, when compared and aligned for maximum correspondence over a comparison window, as measured using [...] sequence comparison algorithms or by manual alignment and visual inspection" (page 15, line 30, through page 16, line 4). The comparison window over which the percent identity necessarily exists is described as "a region of the sequence that is at least about 25 nucleotides [...] in length, or, over a region that

is at least about 50 to 100 nucleotides (page 16, lines 17-19). Moreover, the term "comparison window" is defined as "a segment of any one of the number of contiguous positions selected from the group consisting of from 25 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned" (page 24, lines 15-20). Accordingly, although the polynucleotide sequence listed as SEQ ID NO: 1 is 3,773 nucleotides in length, since the length of the comparison window can vary, the claim does not certainly exclude shorter nucleotide sequences, which cannot be compared directly to SEQ ID NO: 1 over its full length, but which are at least 95% identical to SEQ ID NO: 1 over the length of the comparison window used in determining the percent identity.

Fatyol et al. teaches a stably transformed *Bombyx mori* cell line; see entire document (e.g., the abstract).

Although Fatyol et al. does not teach that the transformed insect cells comprise a nucleic acid sequence having at least 95% identity to SEQ ID NO: 1 that encodes a polypeptide having the amino acid sequence of SEQ ID NO: 2, as evidenced by Huang et al., the cells produce a messenger RNA (mRNA) molecule that encodes a polypeptide having an amino acid sequence that is identical to SEQ ID NO: 2; see, entire document (e.g., page 193, Figure 1B). The USPTO search report "us-10-041-859-2.rge" (result 1 of the "Alignments") shows that the amino acid sequence, which is depicted in Figure 1B and which is present in GenBank™ under accession number AF281073, is identical to the amino acid sequence set forth as SEQ ID NO: 2.

Although Huang et al. does not disclose the polynucleotide sequence of the isolated mRNA encoding the polypeptide of SEQ ID NO: 2, or the polynucleotide sequence of the complementary DNA (cDNA) molecule that was

derived from the mRNA, as evidenced by the USPTO search report "us-10-041-859-1.rge" (result 2 of the "Alignments"), the cDNA has a polynucleotide sequence that is identical to SEQ ID NO: 1; so the isolated mRNA molecule necessarily has a polynucleotide sequence that is identical to the RNA equivalent of the complement of SEQ ID NO: 1.

As further evidenced by the USPTO search report "us-10-041-859-1.rge", a region of the deoxyribonucleotide sequence set forth as SEQ ID NO: 1, which is 2,716 nucleotides in length, is 100% identical to a region of the polynucleotide sequence set forth as "Bombyx mori inhibitor of apoptosis (IAP) mRNA, complete cds" in the database GenBank™ under the accession number AF281073. Accordingly, following an optimal alignment of the two polynucleotide sequences, it was determined by visual inspection that over the length of a comparison window of 2,716 nucleotides, the two polynucleotides are at least 95% identical, since the nucleotide sequences are identical within the comparison window. Because the nucleotide sequence of the prior art is shorter than the nucleotide sequence set forth as SEQ ID NO: 1, the percent identity over a comparison window embracing the full length of SEQ ID NO: 1 cannot be performed by visual inspection; it can only be performed using a comparison window the size of the smaller nucleic acid molecule. Nevertheless, SEQ ID NO: 1 is 100% identical to the polynucleotide sequence of the prior art over the entire length of its shorter sequence.

Giving the claims the broadest reasonable interpretation that is consistent with the plain meaning of the terms therein, unless those terms are defined in the specification, and which is consistent with the supporting disclosure, but without unnecessarily importing limitations into the claims, the claims read on a transformed cell comprising a mRNA molecule encoding the polypeptide of SEQ ID NO: 2. The specification defines the term "nucleic acid" as inclusive of DNA or RNA forms, single- or double-stranded, and coding or non-coding forms.

Although SEQ ID NO: 1 depicts a DNA sequence, the specification further defines the term "nucleic acid sequence" as a term that is interchangeable with the terms mRNA and cDNA. Therefore, as would be interpreted by one ordinarily skilled in the art, since the form of the claimed "nucleic acid sequence" can be that of a DNA or RNA molecule, or that of a coding or non-coding sequence, the claims encompass a nucleic acid comprising a deoxyribonucleotide sequence, the complement thereof, and the corresponding ribonucleotide sequence, which is complementary to the coding sequence, or the same as its complement, except that it is an oligomer of ribonucleotides, rather than deoxyribonucleotides. Furthermore, where the claimed nucleic acid molecule is a ribonucleotide, it would be understood that the molecule must comprise a ribonucleotide sequence that is at least 95% identical, not to SEQ ID NO: 1 or its complement, but to the ribonucleotide equivalent of SEQ ID NO: 1 or its complement. Because the claimed nucleic acid molecule has a sequence that is not necessarily the same length as SEQ ID NO: 1, and because the comparison window can vary, the claims would be interpreted to encompass such a ribonucleotide comprising a sequence that is at least 95% identical over some portion of the molecule, as defined in the specification, to the ribonucleotide equivalent of SEQ ID NO: 1 or its complement after an alignment of the sequences.

Accordingly, giving the claims the broadest reasonable interpretation that that is consistent with the supporting disclosure, the transformed cell of the prior art, which comprises a mRNA molecule encoding the polypeptide of SEQ ID NO: 2, is deemed the same as the claimed invention, absent a showing of any difference, because the transformed cell of the prior art appears identical to a transformed cell comprising a nucleic acid sequence that is at least 95% identical to SEQ ID NO: 1, as defined by the specification. See MPEP § 2112.

Allowable Subject Matter

13. Claims 7 and 8 are allowed.

14. Claim 12 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

15. Claims 1-6, 9-11, 13-19, 44, and 46 are not allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
February 14, 2005